Missouri Department of Health & Senior Services

Health Alert

December 12, 2001

Updated HA# 27

FROM: **MAUREEN E. DEMPSEY, M.D.**
DIRECTOR

SUBJECT: **UPDATED INFORMATION ON ANTHRAX PROPHYLAXIS AND TREATMENT**

The Department of Health and Senior Services is forwarding the following information from CDC. **IT IS IMPORTANT TO WIDELY DISTRIBUTE THIS UPDATE TO PHYSICIANS, EMERGENCY MEDICINE DIRECTORS, URGENT CARE CENTERS AND INFECTION CONTROL PRACTITIONERS.**

CDC has provided information on adverse events associated with anthrax prophylaxis. The new information is noted in bold face type and color on pages 4 and 5 in the attached document.
(Reference CDC. *MMWR* 2001; 50(47): 1031-4.).

Replace previous copy of Health Alert 27 and attachment dated November 16, 2001 with this cover page and accompanying attachment dated December 12, 2001.

Please contact the Department if you have any questions at 1-800-392-0272.

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CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

MISSOURI DEPARTMENT OF HEALTH AND SENIOR SERVICES dhss

FROM: Maureen E. Dempsey, M.D., Director
Missouri Department of Health and Senior Services

SUBJECT: **UPDATED** HA#27 ATTACHMENT: ANTHRAX PROPHYLAXIS AND TREATMENT

DATE: December 12, 2001

***** Urgent Notice *****

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Additional recommendations regarding the initiation and continuation of antimicrobial prophylaxis to prevent inhalational anthrax are found in Health Alert 29.

Health Alert 29 also contains information on distinguishing influenza-like illness from inhalational anthrax.

Interim Recommendations for Postexposure Prophylaxis for Prevention of Inhalational Anthrax After Intentional Exposure to *Bacillus anthracis*

TABLE 1. Interim recommendations for postexposure prophylaxis for prevention of inhalational anthrax after intentional exposure to *Bacillus anthracis*

Category	Initial therapy	Duration
Adults (including pregnant women and immunocompromised persons)	Ciprofloxacin 500 mg po BID or Doxycycline 100 mg po BID	60 days
Children	Ciprofloxacin 10–15 mg/kg po Q12 hrs* or Doxycycline: >8 yrs and >45 kg: 100 mg po BID >8 yrs and ≤45 kg: 2.2 mg/kg po BID ≤8 yrs: 2.2 mg/kg po BID	60 days

*Ciprofloxacin dose should not exceed 1 gram per day in children.

Postexposure prophylaxis is indicated to prevent inhalational anthrax after a confirmed or suspected aerosol exposure. When no information is available about the anti-microbial susceptibility of the implicated strain of *B. anthracis*, initial therapy with ciprofloxacin or doxycycline is recommended for adults and children (Table 1). Use of tetracyclines and fluoroquinolones in children has adverse effects. The risks for these adverse effects must be weighed carefully against the risk for developing life-threatening disease. As soon as penicillin susceptibility of the organism has been confirmed, prophylactic therapy for children should be changed to oral amoxicillin 80 mg/kg of body mass per day divided every 8 hours (not to exceed 500 mg three times daily). *B. anthracis* is not susceptible to cephalosporins or to trimethoprim/sulfamethoxazole, and these agents should not be used for prophylaxis. [CDC. *MMWR* 2001;50(41):893.]

Ciprofloxacin vs. Doxycycline

Previous guidelines (Table 1) recommended ciprofloxacin for antimicrobial prophylaxis until antimicrobial susceptibility test data was available. Isolates involved in the current bioterrorism attacks have been susceptible to ciprofloxacin, doxycycline, and several other antimicrobial agents. Considerations for choosing an antimicrobial agent include effectiveness, resistance, side effects, and cost. No evidence demonstrates that ciprofloxacin is more or less effective than doxycycline for antimicrobial prophylaxis to *B. anthracis*. Widespread use of any antimicrobial will promote resistance. Many common pathogens are already resistant to tetracyclines such as doxycycline. However, fluoroquinolone resistance is not yet common in these same organisms. To preserve the effectiveness of fluoroquinolone against other infections, use of doxycycline for prevention of *B. anthracis* infection among populations at risk may be preferable. However, the selection of the antimicrobial agent for an individual patient should be based on side-effect profiles, history of reactions, and the clinical setting. [CDC. *MMWR* 2001;50(43):948.]

Antimicrobial Prophylaxis In Asymptomatic Pregnant Women After Exposure To *B. anthracis*

The antimicrobial of choice for initial prophylactic therapy among asymptomatic pregnant women exposed to *Bacillus anthracis* is ciprofloxacin, 500 mg twice a day for 60 days. In instances in which the specific *B. anthracis* strain has been shown to be penicillin-sensitive, prophylactic therapy with amoxicillin, 500 mg three times a day for 60 days, may be considered. Isolates of *B. anthracis* implicated in the current bioterrorist attacks are susceptible to penicillin in laboratory tests, but may contain penicillinase activity. Pencillins are not recommended for treatment of anthrax, where such penicillinase activity may decrease their effectiveness. However, penicillins are likely to be effective

for preventing anthrax, a setting where relatively few organisms are present. Doxycycline should be used with caution in asymptomatic pregnant women and only when contraindications are indicated to the use of other appropriate antimicrobial drugs. Pregnant women are likely to be among the increasing number of persons receiving antimicrobial prophylaxis for exposure to *B. anthracis*. Clinicians, public health officials, and women who are candidates for treatment should weigh the possible risks and benefits to the mother and fetus when choosing an antimicrobial for postexposure anthrax prophylaxis. Women who become pregnant while taking antimicrobial prophylaxis should continue the medication and consult a health-care provider or public health official to discuss these issues. No formal clinical studies of ciprofloxacin have been performed during pregnancy. Based on limited human information, ciprofloxacin use during pregnancy is unlikely to be associated with a high risk for structural malformations in fetal development. Data on ciprofloxacin use during pregnancy from the Teratogen Information System indicate that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk, but data are insufficient to determine that there is no risk. Doxycycline is a tetracycline antimicrobial. Potential dangers of tetracyclines to fetal development include risk for dental staining of the primary teeth and concern about possible depressed bone growth and defective dental enamel. Rarely, hepatic necrosis has been reported in pregnant women using tetracyclines. Penicillins generally are considered safe for use during pregnancy and are not associated with an increased risk for fetal malformation. Pregnant women should be advised that congenital malformations occur in approximately 2%–3% of births, even in the absence of known teratogenic exposure. [CDC. *MMWR* 2001;50(43):960.]

Antimicrobial Prophylaxis In Children And Breastfeeding Mothers

Ciprofloxacin or doxycycline is recommended for antimicrobial prophylaxis and treatment of adults and children with *Bacillus anthracis* infection associated with the recent bioterrorist attacks in the United States. Amoxicillin is an option for antimicrobial prophylaxis for children and pregnant women and to complete treatment of cutaneous disease when *B. anthracis* is susceptible to penicillin, as is the case in the recent attacks. Use of ciprofloxacin or doxycycline might be associated with adverse effects in children, and liquid formulations of these drugs are not widely available. This notice provides further information about prophylaxis of children and breastfeeding mothers, including the use of amoxicillin.

Ciprofloxacin, doxycycline, and penicillin G procaine have been effective as antimicrobial prophylaxis for inhalational *B. anthracis* infection in nonhuman primates and are approved for this use in humans by the Food and Drug Administration (FDA). Amoxicillin has not been studied in animal models and is not approved by FDA for the prophylaxis or treatment of anthrax. Other data indicate that *B. anthracis* strains produce a cephalosporinase and suggest that the strains contain an inducible beta-lactamase that might decrease the effectiveness of penicillins, especially when a large number of organisms is present. In addition, penicillin achieves low intracellular concentrations that might be detrimental to its ability to kill germinating spores in macrophages.

Because of these concerns, penicillins (including amoxicillin) are not recommended for initial treatment of anthrax, but are likely to be effective for antimicrobial prophylaxis following exposure to *B. anthracis*, a setting where relatively few organisms are expected to be present. Therefore, amoxicillin* may be used for the 60-day antimicrobial prophylaxis in infants and children when the isolate involved in the exposure is determined to be susceptible to penicillin. Isolates of *B. anthracis* implicated in the recent bioterrorist attacks are susceptible to ciprofloxacin, doxycycline, and penicillin.

Because of its known safety for infants, amoxicillin is an option for antimicrobial prophylaxis in breastfeeding mothers when *B. anthracis* is known to be penicillin-susceptible and no contraindication to maternal amoxicillin use is indicated. The American Academy of Pediatrics also

considers ciprofloxacin and tetracyclines (which include doxycycline) to be usually compatible with breastfeeding because the amount of either drug absorbed by infants is small, but little is known about the safety of long-term use. Mothers concerned about the use of ciprofloxacin or doxycycline for antimicrobial prophylaxis should consider expressing and then discarding breast milk so that breastfeeding can be resumed when antimicrobial prophylaxis is completed. Decisions about antimicrobial choice and continuation of breastfeeding should be made by the mother and her and the infant's health-care providers. Consideration should be given to antimicrobial efficacy, safety for the infant, and the benefits of breastfeeding. Health-care providers prescribing antimicrobial drugs for the prophylaxis or treatment of anthrax should be aware of their adverse effects and consult with an infectious disease specialist as needed. Additional information about recognition, prophylaxis, and treatment of anthrax infection is available at http://www.bt.cdc.gov.

*The recommended dose of amoxicillin is 80 mg/kg/day orally divided every 8 hours (maximum 500 mg/dose).

[CDC. *MMWR* 2001;50(45):1014-6.]

Basis for Initiating Prophylaxis

The exposure circumstances are the most important factors that direct decisions about prophylaxis. Persons with an exposure or contact with an item or environment known, or suspected to be contaminated with *B. anthracis* — regardless of laboratory tests results — should be offered antimicrobial prophylaxis. Exposure or contact, not laboratory test results, is the basis for initiating such treatment. Culture of nasal swabs is used to detect anthrax spores. Nasal swabs can occasionally document exposure, but cannot rule out exposure to *B. anthracis*. As an adjunct to epidemiologic evaluations, nasal swabs may provide clues to help assess the exposure circumstances. In addition, rapid evaluation of contaminated powder, including particle size and characteristics, may prove useful in assessing the risk for inhalational anthrax. [CDC. *MMWR* 2001;50(42):916.]

Use of High-Dose Penicillins for Prophylaxis

High-dose penicillin (e.g., amoxicillin or penicillin VK) may be an option for antimicrobial prophylaxis when ciprofloxacin or doxycycline are contraindicated. The likelihood of beta-lactamase induction events that would increase the penicillin MIC is lower when only small numbers of vegetative cells are present, such as during antimicrobial prophylaxis. [CDC. *MMWR* 2001;50(42):919.]

*** Adverse Events Associated with Anthrax Prophylaxis ***

Antimicrobial prophylaxis to prevent inhalational anthrax has been recommended for persons potentially exposed to *Bacillus anthracis* as a result of the recent bioterrorist attacks. During October 26–November 6, 2001, an epidemiologic evaluation to detect adverse events associated with antimicrobial prophylaxis was conducted among 8,424 postal employees who had been offered antimicrobial prophylaxis for 60 days in New Jersey (NJ), New York City (NYC), and one postal facility in the District of Columbia (DC). This report summarizes preliminary results of that evaluation, which found that few employees receiving antimicrobial prophylaxis sought medical attention for symptoms that may have been associated with anaphylaxis.

In NJ, NYC, and DC, a questionnaire was administered on days 7 to 10 after postal employees received prophylaxis (when they returned for medication refills). In NYC and DC, the questionnaire was self-administered by postal employees; in NJ, nurses interviewed postal workers and administered the questionnaire. . . . . Of the 8,424 postal employees offered antimicrobial prophylaxis, 5,819 (69%) completed or were administered the questionnaire to evaluate the occurrence of adverse events. A total of 3,863 (66%) had initiated antimicrobial prophylaxis; of these, 3,428 (89%) reported using ciprofloxacin for antimicrobial prophylaxis;

435 (11%) used other antimicrobials (when ciprofloxacin was contraindicated), including doxycycline (6%) and amoxicillin (1%) (Table 1).

Of the 3,428 persons on ciprofloxacin:

- **666 (19%) reported severe nausea, vomiting, diarrhea, or abdominal pain;**
- **484 (14%) reported fainting, light-headedness, or dizziness;**
- **250 (7%) reported heartburn or acid reflux; and**
- **216 (6%) reported rashes, hives, or itchy skin.**

Of those persons taking ciprofloxacin, 287 (8%) discontinued the medication:

- **116 (3%) discontinued the medication because of adverse events,**
- **27 (1%) discontinued because of fear of possible adverse events, and**
- **28 (1%) stopped taking the drug because they "did not think it was needed."**

For the 3,863 persons on any medication for antimicrobial prophylaxis, 83 (2%) sought medical attention for symptoms that may have been associated with anaphylaxis. Among the 33 persons who sought medical attention for these symptoms in NJ and NYC, none was hospitalized and none of the symptoms was attributed to antimicrobial prophylaxis by clinicians who evaluated these persons. Follow-up of persons in DC who sought medical attention for symptoms that may have been associated with anaphylaxis is ongoing.

TABLE 1. Number and percentage of postal employees who reported adverse events 7 to 10 days after receiving anthrax prophylaxis — New Jersey (NJ), New York City (NYC), and the District of Columbia (DC) Metropolitan Area, October 26–November 6, 2001

Antimicrobial and site	No. persons on prophylaxis	Reported severe nausea, vomiting, diarrhea, or abdominal pain		Reported fainting, light-headedness, or dizziness		Reported heartburn or acid reflux		Reported rash, hives, or itchy skin		Required follow-up because of adverse events*		Required hospitalization		Discontinued prophylaxis because of adverse events	
		No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Ciprofloxacin	3,428														
NJ	365	94	(26)	46	(13)	47	(13)	43	(12)	4	(1)	0	(0)	26	(7)
NYC	1,612	231	(14)	166	(10)	89	(6)	86	(5)	25	(2)	0	(0)	63	(4)
DC	1,451	341	(24)	272	(19)	114	(8)	87	(6)	42	(3)	NA†		27	(2)
Doxycycline	232														
NJ	55	10	(18)	4	(7)	11	(20)	6	(11)	2	(4)	0	(0)	0	(0)
NYC	96	11	(11)	1	(1)	4	(4)	2	(2)	2	(2)	0	(0)	1	(1)
DC	81	10	(12)	12	(15)	4	(5)	4	(5)	7	(9)	NA		5	(6)

* Persons who required detailed follow-up reported difficulty breathing; throat tightness and difficulty swallowing; swelling of lips, tongue, or face; or rash, hives, or itchy skin, and sought medical attention for their symptoms.
† Not available.

Editorial Note: Among persons with exposures to *B. anthracis* related to the recent bioterrorist attacks, completion of a full 60-day course of antimicrobial prophylaxis is essential for preventing anthrax. . . . . Although adverse events were commonly reported by postal employees who participated in this evaluation and included gastrointestinal and dermatologic reactions, only 2% of persons surveyed sought medical care for symptoms that may have been associated with anaphylaxis. Overall rates of adverse events (regardless of attributability) in NJ, NYC, and DC are similar to the frequency of adverse events among other persons on antimicrobial prophylaxis for exposures to *B. anthracis* related to these bioterrorist attacks and among persons on ciprofloxacin therapy for any indication. The higher rates of adverse events in NJ compared with NYC and DC (p=0.001), may be explained by the different mode of administration of the questionnaires (nurse versus self-administered). Discontinuation of therapy caused by adverse events was similar to other groups previously studied.

[CDC. *MMWR* 2001;50(47):1031-4.]

Patient Information: Ciprofloxacin 500 mg
ORAL TABLET 55000

This drug belongs to a class of drugs called quinolone antibiotics. You have been given this drug for protection against possible exposure to an infection-causing bacteria. This drug prevents:
* Anthrax

You have been provided a limited supply of medicine. Local emergency health workers or your healthcare provider will inform you if you need more medicine after you finish this supply. If so, upon your follow-up visit, you will be told how to get more medicine. You will be told if no more medicine is needed. You may also be switched from this medicine to a different medicine based on laboratory tests.

Take this medicine as prescribed: one tablet by mouth, two times a day.

You will be provided special dosing instructions for children.

Keep taking your medicine, even if you feel okay, unless your doctor tells you to stop. If you stop taking this medicine too soon, you may become ill.

You should take this medicine with a full glass of water. Drink several glasses of water each day while you are taking this medicine. It is best to take this medicine 2 hours after a meal. If it upsets your stomach, you may take it with food, but do not take it with milk, yogurt, or cheese.

If you miss a dose, take the missed dose as soon as possible. If it is almost time for your next regular dose, wait until then to take your medicine, and skip the missed dose. Do not take two doses at the same time.

DRUGS AND FOODS TO AVOID: Do not take the following drugs within 2 hours of taking Ciprofloxocin: antacids such as Maalox or Mylanta, vitamins, iron supplements, zinc supplements, or sucralfate (Carafate). You may take them 2 hours after or 6 hours before Ciprofloxocin. Also, make sure your doctor knows if you are taking asthma medicine like theophylline, gout medicine like probenecid (Benemid), or a blood thinner such as Coumadin.

Avoid drinking more than one or two caffeinated beverages (coffee, tea, soft drinks) per day. Avoid taking this medicine with foods containing large amounts of calcium, like milk, yogurt, or cheese.

WARNINGS: If you have epilepsy or kidney disease, or if you are pregnant, become pregnant, or are breastfeeding, notify emergency healthcare workers before you start taking this medicine.

Do not take this medicine if you have had an allergic reaction to ciprofloxacin or other quinolone medicines such as norfloxacin (Noroxin), ofloxacin (Floxin) or nalidixic acid (NegGram).

This medicine may make you dizzy or lightheaded. Avoid driving or using machinery until you know how it will affect you.

This medicine increases the chance of sunburn; make sure to use sunscreen to protect your skin.

SIDE EFFECTS: Call your doctor or seek medical advice right away if you are having any of these side effects: rash or hives; swelling of face, throat, or lips; shortness of breath or trouble breathing; seizures; or severe diarrhea. Less serious side effects include nausea, mild diarrhea, stomach pain, dizziness, and headache. Talk with your doctor if you have problems with these side effects.

(CDC Health Advisory. Use of ciprofloxacin or doxycycline for postexposure prophylaxis for prevention of inhalational anthrax, October 31, 2001.)

Patient Information:**Doxycycline** 100 MG
ORAL TABLET

This drug belongs to a class of drugs called tetracycline antibiotics. You have been given this drug for protection against possible exposure to an infection-causing bacteria. This drug prevents:
* Anthrax

You have been provided a limited supply of medicine. Local emergency health workers or your healthcare provider will inform you if you need more medicine after you finish this supply. If so, upon your follow-up visit, you will be told how to get more medicine. You will be told if no more medicine is needed. You may also be switched from this medicine to a different medicine based on laboratory tests.

Take this medicine as prescribed: one tablet by mouth, two times a day.

You will be provided special dosing instructions for treatment of children under 8 years of age.

Keep taking your medicine, even if you feel okay, unless your healthcare provider tells you to stop. If you stop taking this medicine too soon, you may become ill.

You may take your medicine with or without food or milk, but food or milk may help you avoid stomach upset.

If you miss a dose, take the missed dose as soon as possible. If it is almost time for your next regular dose, wait until then to take your medicine, and skip the missed dose. Do not take two doses at the same time.

DRUGS AND FOODS TO AVOID: Do not take the following medicines within 2 hours of taking DOXYCYCLINE: antacids such as Maalox or Mylanta, calcium or iron supplements, cholestyramine (Questran) or colestipol (Colestid).

While you are taking this medicine, birth control pills may not work as well; make sure to use another form of birth control.

WARNINGS: If you have liver disease, or if you are or might be pregnant, or if you are breastfeeding, tell emergency healthcare workers before you start taking this medicine.

This medicine increases the chance of sunburn; make sure to use sunscreen to protect your skin.

Do not take this medicine if you have had an allergic reaction to any tetracycline antibiotics.

Women may have vaginal yeast infections from taking this medicine.

SIDE EFFECTS: Call your doctor or seek medical attention right away if you are having any of these side effects: skin rash, hives, or itching; wheezing or trouble breathing; swelling of the face, lips, or throat. Less serious side effects include diarrhea, upset stomach, nausea, sore mouth or throat, sensitivity to sunlight, or itching of the mouth or vagina lasting more than 2 days. Talk with your doctor if you have problems with these side effects.

(CDC Health Advisory. Use of ciprofloxacin or doxycycline for postexposure prophylaxis for prevention of inhalational anthrax, October 31, 2001.)

Inhalational Anthrax Treatment Protocol for Cases Associated With the October 2001, Bioterrorism Attack

TABLE 1. Inhalational anthrax treatment protocol*,† for cases associated with this bioterrorism attack

Category	Initial therapy (intravenous)§,¶	Duration
Adults	Ciprofloxacin 400 mg every 12 hrs* **or** Doxycycline 100 mg every 12 hrs†† **and** One or two additional antimicrobials¶	IV treatment initially**. Switch to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 500 mg po BID **or** Doxycycline 100 mg po BID Continue for 60 days (IV and po combined)§§
Children	Ciprofloxacin 10–15 mg/kg every 12hrs ¶¶,*** **or** Doxycycline:†††,†† >8 yrs and >45 kg: 100 mg every 12 hrs >8 yrs and ≤45 kg: 2.2 mg/kg every 12 hrs ≤8 yrs: 2.2 mg/kg every 12 hrs **and** One or two additional antimicrobials¶	IV treatment initially**. Switch to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 10–15 mg/kg po every 12 hrs*** **or** Doxycycline:††† >8 yrs and >45 kg: 100 mg po BID >8 yrs and ≤45 kg: 2.2 mg/kg po BID ≤8 yrs: 2.2 mg/kg po BID Continue for 60 days (IV and po combined)§§
Pregnant women§§§	Same for nonpregnant adults (the high death rate from the infection outweighs the risk posed by the antimicrobial agent)	IV treatment initially. Switch to oral antimicrobial therapy when clinically appropriate.† Oral therapy regimens same for nonpregnant adults
Immunocompromised persons	Same for nonimmunocompromised persons and children	Same for nonimmunocompromised persons and children

* For gastrointestinal and oropharyngeal anthrax, use regimens recommended for inhalational anthrax.

† Ciprofloxacin or doxycycline should be considered an essential part of first-line therapy for inhalational anthrax.

§ Steroids may be considered as an adjunct therapy for patients with severe edema and for meningitis based on experience with bacterial meningitis of other etiologies.

¶ Other agents with *in vitro* activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. Because of concerns of constitutive and inducible beta-lactamases in *Bacillus anthracis*, penicillin and ampicillin should not be used alone. Consultation with an infectious disease specialist is advised.

** Initial therapy may be altered based on clinical course of the patient; one or two antimicrobial agents (e.g., ciprofloxacin or doxycycline) may be adequate as the patient improves.

†† If meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration.

§§ Because of the potential persistence of spores after an aerosol exposure, antimicrobial therapy should be continued for 60 days.

¶¶ If intravenous ciprofloxacin is not available, oral ciprofloxacin may be acceptable because it is rapidly and well absorbed from the gastrointestinal tract with no substantial loss by first-pass metabolism. Maximum serum concentrations are attained 1–2 hours after oral dosing but may not be achieved if vomiting or ileus are present.

*** In children, ciprofloxacin dosage should not exceed 1 g/day.

††† The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (e.g., Rocky Mountain spotted fever).

§§§ Although tetracyclines are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose related; therefore, doxycycline might be used for a short time (7–14 days) before 6 months of gestation.

A high index of clinical suspicion and rapid administration of effective antimicrobial therapy is essential for prompt diagnosis and effective treatment of anthrax. Limited clinical experience is available and no controlled trials in humans have been performed to validate current treatment recommendations for inhalational anthrax. Based on studies in nonhuman primates and other animal and in vitro data, ciprofloxacin or doxycycline should be used for initial intravenous therapy until antimicrobial susceptibility results are known (Table 1). Because of the mortality associated with inhalational anthrax, two or more antimicrobial agents predicted to be effective are recommended; however, controlled studies to support a multiple drug approach are not available. Other agents with in vitro activity suggested for use in conjunction with ciprofloxacin or doxycycline include rifampin, vancomycin, imipenem, chloramphenicol, penicillin and ampicillin, clindamycin, and clarithromycin; but other than for penicillin, limited or no data exist regarding the use of these agents in the treatment of inhalational *B. anthracis* infection. Cephalosorins and trimethoprim-sulfamethoxazole should not be used for therapy. Regimens being used to treat patients described in this report include ciprofloxacin, rifampin, and vancomycin; and ciprofloxacin, rifampin, and clindamycin.

Penicillin is labelled for use to treat inhalational anthrax. However, preliminary data indicate the presence of constitutive and inducible beta-lactamases in the *B. anthracis* isolates from Florida, NYC, and DC. Thus, treatment of systemic *B. anthracis* infection using a penicillin alone (i.e., penicillin G and ampicillin) is not recommended. The *B. anthracis* genome sequence shows that this organism encodes two beta-lactamases: a penicillinase and a cephalosporinase. Data in the literature also show that some beta-lactamase negative *B. anthracis* strains for which the penicillin MICs are 0.06 µg/mL increase to 64 µg/mL and become beta-lactamase positive when exposed to semisynthetic penicillins. The frequency of this induction event is unknown. Although amoxicillin/clavulanic acid is more active than amoxicillin alone against beta-lactamase, producing strains in vitro, the combination may not be clinically effective for inhalational anthrax where large numbers of organisms are likely to be present.

Toxin-mediated morbidity is a major complication of systemic anthrax. Corticosteroids have been suggested as adjunct therapy for inhalational anthrax associated with extensive edema, respiratory compromise, and meningitis

[CDC. *MMWR* 2001;50(42):916-8.]

Treatment of Children

Ciprofloxacin or doxycycline is recommended for antimicrobial prophylaxis and treatment of adults and children with *Bacillus anthracis* infection associated with the recent bioterrorist attacks in the United States. Amoxicillin is an option for antimicrobial prophylaxis for children and pregnant women and to complete treatment of cutaneous disease when *B. anthracis* is susceptible to penicillin, as is the case in the recent attacks. Use of ciprofloxacin or doxycycline might be associated with adverse effects in children, and liquid formulations of these drugs are not widely available. This notice provides further information about treatment of children, including the use of amoxicillin.

Amoxicillin has not been studied in animal models and is not approved by FDA for the prophylaxis or treatment of anthrax. Other data indicate that *B. anthracis* strains produce a cephalosporinase and suggest that the strains contain an inducible beta-lactamase that might decrease the effectiveness of penicillins, especially when a large number of organisms is present. In addition, penicillin achieves low intracellular concentrations that might be detrimental to its ability to kill germinating spores in macrophages. Because of these concerns, penicillins (including amoxicillin) are not recommended for initial treatment of anthrax, but are likely to be effective for antimicrobial prophylaxis following exposure to *B. anthracis*, a setting where relatively few organisms are expected to be present.

Initial treatment of infants and children with inhalational or systemic (including gastrointestinal or oropharyngeal) anthrax should consist of intravenous ciprofloxacin[†] or doxycyline[§] , plus one or two additional antimicrobial[¶] agents. If meningitis is suspected, ciprofloxacin might be more effective than doxycycline because of better central nervous system penetration. Experience with fluoroquinolones other than ciprofloxacin in children is limited.

After clinical improvement following intravenous treatment for inhalational or cutaneous anthrax, oral therapy with one or two antimicrobial agents (including either ciprofloxacin or doxycycline) may be used to complete the first 14–21 days of treatment for inhalational anthrax or the first 7–10 days for uncomplicated cutaneous anthrax. The optimal oral treatment regimen is unknown; some adults with inhalational anthrax as a result of the recent bioterrorist attacks are receiving ciprofloxacin and rifampin. For both inhalational and cutaneous anthrax in the setting of this bioterrorist attack, antimicrobial therapy should be continued for 60 days because of the likelihood of exposure to aerosolized *B. anthracis* and the need to protect against persistent spores that might germinate in the respiratory tract. Because of potential adverse effects of prolonged use of ciprofloxacin or doxycycline in children, amoxicillin is an option for completion of the remaining 60 days of therapy for persons infected in these bioterrorist attacks.

Health-care providers prescribing antimicrobial drugs for the prophylaxis or treatment of anthrax should be aware of their adverse effects and consult with an infectious disease specialist as needed. Additional information about recognition, prophylaxis, and treatment of anthrax infection is available at http://www.bt.cdc.gov.

† The recommended dose of ciprofloxacin is 10 mg/kg/dose every 12 hours intravenously (maximum 400 mg/dose) or 15 mg/kg/dose every 12 hours orally (maximum 500 mg/dose).
§ The recommended dose of doxycycline is 2.2 mg/kg/dose every 12 hours intravenously or orally (maximum 100 mg/dose).
¶ Options for additional drugs, based on in vitro sensitivity testing of isolates in the recent attacks, include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin.

[CDC. *MMWR* 2001;50(45):1014-6.]

Cutaneous Anthrax Treatment Protocol* for Cases Associated With the October 2001, Bioterrorism Attack

TABLE 2. Cutaneous anthrax treatment protocol* for cases associated with this bioterrorism attack

Category	Initial therapy (oral)†	Duration
Adults*	Ciprofloxacin 500 mg BID **or** Doxycycline 100 mg BID	60 days§
Children*	Ciprofloxacin 10–15 mg/kg every 12 hrs (not to exceed 1 g/day)† **or** Doxycycline:¶ >8 yrs and >45 kg: 100 mg every 12 hrs >8 yrs and ≤45 kg: 2.2 mg/kg every 12 hrs ≤8 yrs: 2.2 mg/kg every 12 hrs	60 days§
Pregnant women*,**	Ciprofloxacin 500 mg BID **or** Doxycycline 100 mg BID	60 days§
Immunocompromised persons*	Same for nonimmunocompromised persons and children	60 days§

* Cutaneous anthrax with signs of systemic involvement, extensive edema, or lesions on the head or neck require intravenous therapy, and a multidrug approach is recommended. Table 1.
† Ciprofloxacin or doxycycline should be considered first-line therapy. Amoxicillin 500 mg po TID for adults or 80 mg/kg/day divided every 8 hours for children is an option for completion of therapy after clinical improvement. Oral amoxicillin dose is based on the need to achieve appropriate minimum inhibitory concentration levels.
§ Previous guidelines have suggested treating cutaneous anthrax for 7–10 days, but 60 days is recommended in the setting of this attack, given the likelihood of exposure to aerosolized *B. anthracis* (*6*).
¶ The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (e.g., Rocky Mountain spotted fever).
** Although tetracyclines or ciprofloxacin are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose related; therefore, doxycycline might be used for a short time (7–14 days) before 6 months of gestation.

For cutaneous anthrax, ciprofloxacin and doxycycline also are first-line therapy (Table 2). As for inhalational disease, intravenous therapy with a multidrug regimen is recommended for cutaneous anthrax with signs of systemic involvement, for extensive edema, or for lesions on the head and neck (see recommendations for treatment of inhalational anthrax). In cutaneous anthrax, antimicrobial treatment may render lesions culture negative in 24 hours, although progression to eschar formation still occurs. Some experts recommend that corticosteroids be considered for extensive edema or swelling of the head and neck region associated with cutaneous anthrax. Cutaneous anthrax is typically treated for 7–10 days; however, in this bioterrorism attack, the risk for simultaneous aerosol exposure appears to be high. Although infection may produce an effective immune response, a potential for reactivation of latent infection may exist. Therefore, persons with cutaneous anthrax associated with this attack should be treated for 60 days.

[CDC. *MMWR* 2001;50(42):918.]

Treatment of Children

Ciprofloxacin or doxycycline is recommended for antimicrobial prophylaxis and treatment of adults and children with *Bacillus anthracis* infection associated with the recent bioterrorist attacks in the United States. Amoxicillin is an option for antimicrobial prophylaxis for children and pregnant women and to complete treatment of cutaneous disease when *B. anthracis* is susceptible to penicillin, as is the case in the recent attacks. Use of ciprofloxacin or doxycycline might be associated with adverse effects in children, and liquid formulations of these drugs are not widely available. This notice provides further information about treatment of children, including the use of amoxicillin.

Amoxicillin has not been studied in animal models and is not approved by FDA for the prophylaxis or treatment of anthrax. Other data indicate that *B. anthracis* strains produce a cephalosporinase and suggest that the strains contain an inducible beta-lactamase that might decrease the effectiveness of penicillins, especially when a large number of organisms is present. In addition, penicillin achieves low intracellular concentrations that might be detrimental to its ability to kill germinating spores in macrophages. Because of these concerns, penicillins (including amoxicillin) are not recommended for initial treatment of anthrax, but are likely to be effective for antimicrobial prophylaxis following exposure to *B. anthracis*, a setting where relatively few organisms are expected to be present.

Initial treatment of infants and children with inhalational or systemic (including gastrointestinal or oropharyngeal) anthrax should consist of intravenous ciprofloxacin[†] or doxycyline[§] , plus one or two additional antimicrobial[¶] agents. If meningitis is suspected, ciprofloxacin might be more effective than doxycycline because of better central nervous system penetration (2). Experience with fluoroquinolones other than ciprofloxacin in children is limited.

Ciprofloxacin or doxycycline should be the initial treatment of localized cutaneous anthrax in infants and children. Intravenous therapy with multiple antimicrobial agents is recommended for cutaneous anthrax with systemic involvement, extensive edema, or lesions on the head or neck. Whether infants and young children are at increased risk for systemic dissemination of cutaneous infection is not known; a 7-month-old patient infected during the recent bioterrorism attacks developed systemic illness after onset of cutaneous anthrax. For young children (e.g. aged <2 years), initial therapy of cutaneous anthrax should be intravenous, and combination therapy with additional antimicrobials should be considered.

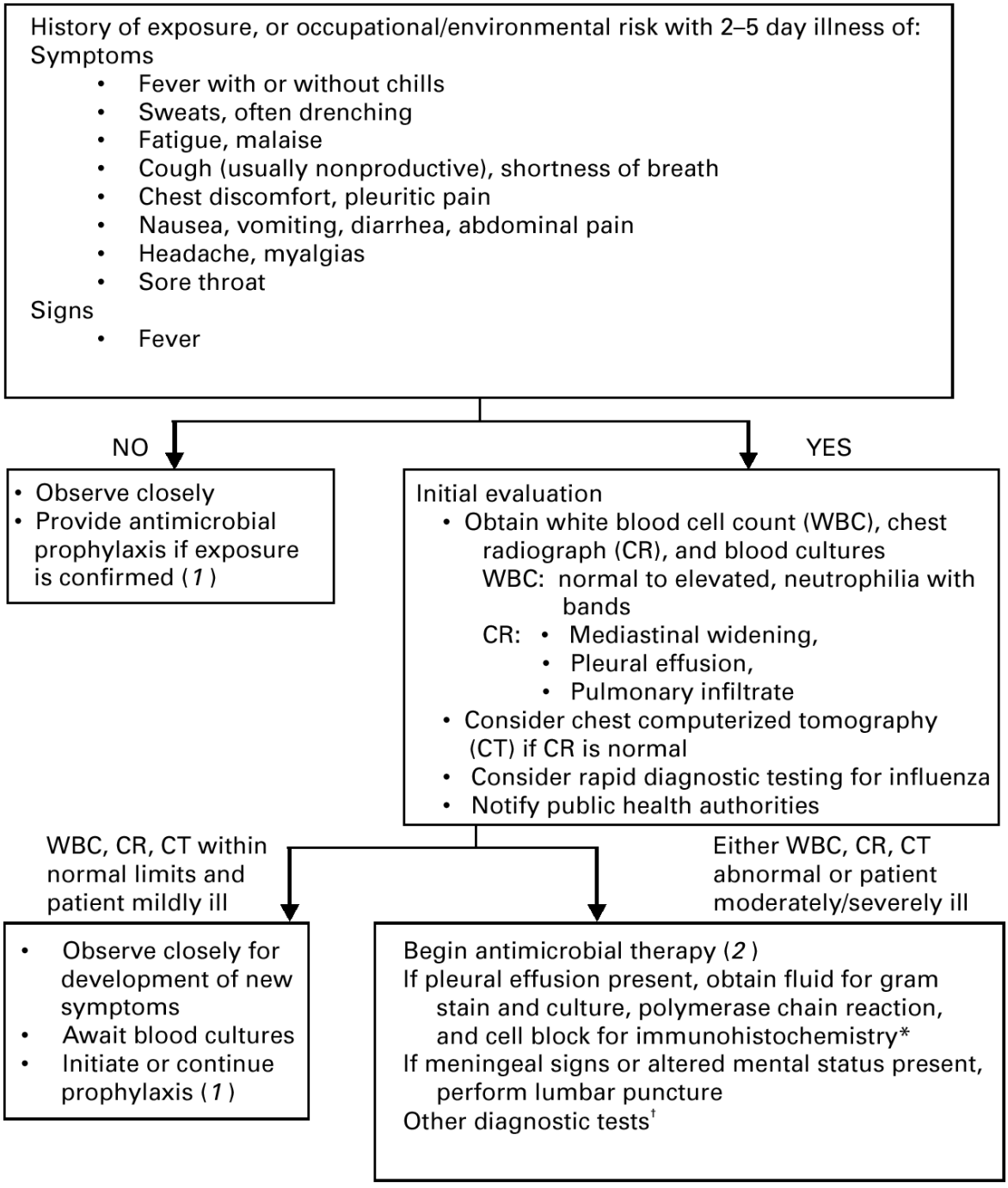
After clinical improvement following intravenous treatment for inhalational or cutaneous anthrax, oral therapy with one or two antimicrobial agents (including either ciprofloxacin or doxycycline) may be used to complete the first 14–21 days of treatment for inhalational anthrax or the first 7–10 days for uncomplicated cutaneous anthrax. The optimal oral treatment regimen is unknown; some adults with inhalational anthrax as a result of the recent bioterrorist attacks are receiving ciprofloxacin and rifampin. For both inhalational and cutaneous anthrax in the setting of this bioterrorist attack, antimicrobial therapy should be continued for 60 days because of the likelihood of exposure to aerosolized *B. anthracis* and the need to protect against persistent spores that might germinate in the respiratory tract. Because of potential adverse effects of prolonged use of ciprofloxacin or doxycycline in children, amoxicillin is an option for completion of the remaining 60 days of therapy for persons infected in these bioterrorist attacks.

Health-care providers prescribing antimicrobial drugs for the prophylaxis or treatment of anthrax should be aware of their adverse effects and consult with an infectious disease specialist as needed. Additional information about recognition, prophylaxis, and treatment of anthrax infection is available at http://www.bt.cdc.gov.

† The recommended dose of ciprofloxacin is 10 mg/kg/dose every 12 hours intravenously (maximum 400 mg/dose) or 15 mg/kg/dose every 12 hours orally (maximum 500 mg/dose).
§ The recommended dose of doxycycline is 2.2 mg/kg/dose every 12 hours intravenously or orally (maximum 100 mg/dose).
¶ Options for additional drugs, based on in vitro sensitivity testing of isolates in the recent attacks, include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin.

[CDC. *MMWR* 2001;50(45):1014-6.]

Clinical Evaluation of Persons with Possible Inhalational Anthrax
(CDC. *MMWR* 2001;50(43): 945.)

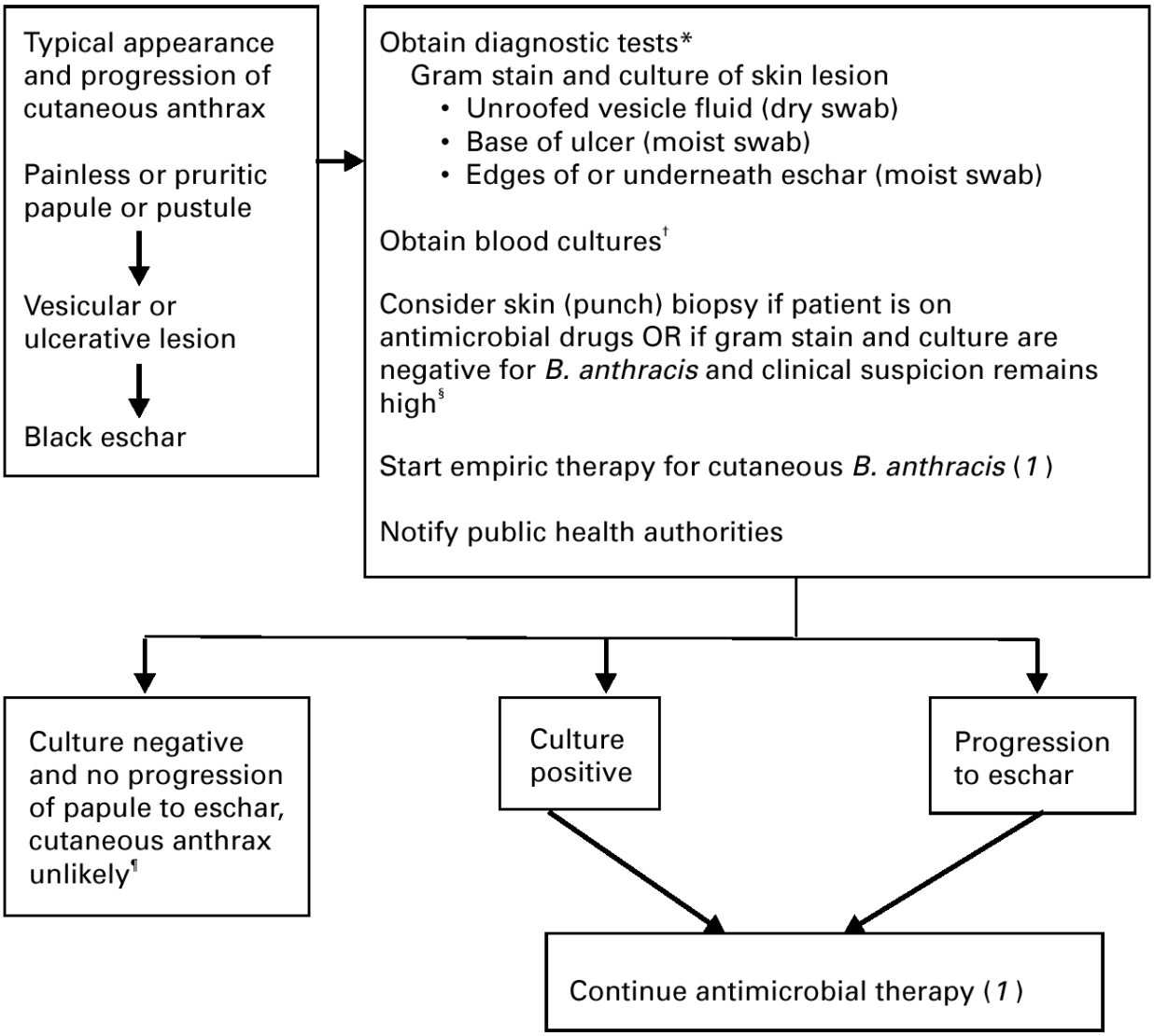


* Available through CDC or LRN. Cell block obtained by centrifugation of pleural fluid.
† Serologic testing available at CDC may be an additional diagnostic technique.

References

1. CDC. Update: investigation of anthrax associated with intentional exposure and interim public health guidelines, October 2001. MMWR 2001;50:889–93.
2. CDC. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. MMWR 2001;50:909–19.

Clinical Evaluation of Persons with Possible Cutaneous Anthrax
(CDC. *MMWR* 2001;50(43): 946.)



* Serologic testing available at CDC may be an additional diagnostic technique for confirmation of cases of cutaneous anthrax.

† If blood cultures are positive for *B. anthracis*, treat with antimicrobials as for inhalational anthrax (*1*).

§ Punch biopsy should be submitted in formalin to CDC. Polymerase chain reaction can also be done on formalin-fixed specimen. Gram stain and culture are frequently negative for *B. anthracis* after initiation of antimicrobials.

¶ Continued antimicrobial prophylaxis for inhalational anthrax for 60 days if aerosol exposure to *B. anthracis* is known or suspected (*2*).

Reference

1. CDC. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. MMWR 2001;50:909–19.
2. CDC. Update: investigation of anthrax associated with intentional exposure and interim public health guidelines, October 2001. MMWR 2001;50:889–93.